26. (Amended) A pharmaceutical composition comprising a soluble [human] H4-1BB of claim 24 in admixture with a suitable diluent, carrier, or excipient.

REMARKS

The office action of February 3, 1997 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is requested. Claims 5-6, 21-22, and 24 through 26 remain in this case, claims 6, 21-22, and 24-26 being amended by this response, with no claims being canceled, or added by way of this response. In addition, the Examiner has maintained a restriction requirement made earlier in the prosecution of this application. Claims 19 and 20 comprise a group of claims not elected by the Applicant for further prosecution and are withdrawn from consideration pending a successful petition of the restriction requirement, or a divisional or CIP application based upon the current disclosure. Through this response the rejections to the application presented by the Examiner, are respectfully traversed. Reconsideration of claims is respectfully requested.

Priority of Application

The Examiner has stated that the current application has, as its appropriate priority date, 9/16/93 the filing date of the parent application 08/122,796, obviating the priority of the current application with regard to the earlier filed parental applications 07/922,996 filed on 7/30/92, or application 07/267,577 (now abandoned) filed on 11/7/88. However, the ultimate parent did provide disclosure of both the cDNA and the amino acid sequence termed "PLD78." This data present in the application filed in 1988 then provides support for the current claims, and a much earlier priority date, by demonstrating that the technology itself was already in the hands of the applicants.

Alternatively, if the Examiner maintains the 1993 date for the effective priority date for this application, the patentability of the claims remains, because as discussed below, the

Schwarz et al., reference relied upon is not a "publication" in the sense of one both available to the public or one that enabled the use of any invention.

Rejection Under 35 U.S.C. §101

The Examiner has rejected claim 6 under 35 U.S.C. § 101 as being directed to non-statutory matter. This claim has been amended to comply with the Examiners concerns regarding the "hand of Man." Given the above amendment, the Examiner's rejection under 35 U.S.C. § 101, regarding claim 6 is respectfully traversed, and reconsideration is respectfully requested.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 5, 21, 24-26 under 35 U.S.C. § 112, first paragraph, as failing to enable anything other for the protein of SEQ. ID. NO.:2, which provides for the sequence of the H4-1BB protein. This rejection is respectfully traversed, and reconsideration is requested.

It is important to remember that a disclosure is sufficiently enabling for the technology it discloses if the prior art, along with the disclosure, provides the necessary teachings to accompany the specification. This is appropriate because, in determining whether the disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, and U.S. patents. The important point is that the relevant prior art acts in a complementary fashion to the disclosure itself. Where the specification reveals the relevant technology, here the H4-1BB sequence, the prior art will support claims using that technology in conjunction with already known protocols and procedures to generate the relevant molecules or utilities -- as claimed in this application (i.e. other examples would be fusion proteins, probes, primers,

use in affinity chromatography to delineate the fine details of the H4-1BB transduction pathway, etc.,). Citation to specific art then acts to incorporate the needed techniques and protocols into the specification for purposes of teaching the technology and the uses to which the invention may be put. Here the specification, and the incorporated art and artisans, teach how to use a the H4-1BB sequence, once it is known as such. Its utility then can be expressed in the limits of the artisans in the field. For the general technology, known to those skilled in the art at the time of filing of the parent application see, Edward S. Golub, IMMUNOLOGY: A SYNTHESIS, p. 72-151(Sinauer Assoc. publ. 1987); David Suzuki, AN INTRODUCTION INTO GENETIC ANALYSIS *passim* (4th ed. 1988); James D. Watson, MOLECULAR BIOLOGY OF THE GENE, p. 832-80 (4th ed. 1987);

With the knowledge of the relevant technology provided by a host of sources in the art, three relevant textbooks being cited above, all before the appropriate 1988 priority date, a given discovery would not only provide a litany of potential uses for those skilled in the art, but would serve to indicate what techniques and steps would be useful to make a more complete use of the discovered technology without forcing every patent application to become either a treatise on the relevant technology or become a lab manual reciting protocols already known by skilled artisans.

With regard to the nature of the specification in the instant matter, the uses or technological steps necessary to make the invention disclosed by the Applicant need not be apparent to everyone, all that is required is that enablement, and the potential usefulness of the discovery is communicated to the skilled artisans of the relevant technology, here the use of a known amino acid sequence bearing more than substantial homology to the mouse 4-1BB and belonging to the superfamily of nerve growth factors. Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882). Respectfully the Applicant maintains that this communication was sufficiently performed in the instant specification, and in its parent applications for all the claims pending in this application.

The point is that the disclosure by the Applicant, and those citations disclosing the state of the art at the time the application was filed are sufficient to demonstrate that the H4-1BB amino acid sequence, once known as such, **does have the utilities pronounced in the specification and can support the relevant claims.** In this way establishing the effectiveness and patentability of the sequence claimed and methods related to its use. Given this, the Examiner's rejections under 35 U.S.C. § 112, first paragraph are respectfully traversed, and reconsideration is respectfully requested.

Patent law has long accepted the concept that while a specification must disclose the critical aspects of an invention to be patentable, here the exact amino acid sequence of the H4--1BB protein, some experimentation may be both necessary and allowed to determine the proper use of an invention in a given context. In the instant application the question for routine experimentation is the exact size or specifics of molecular domains or the precise interactions of the extracellular domain which the H4-1BB exhibits with its ligands.

The important aspect to remember is that even though *some* experimentation may be needed this does not indicate that the patent lacks enablement in any way. The appropriate standard is as to whether that experimentation is ***undue***. In this determination, guidance should be taken from the ***In re Wands*** case. 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). This is the leading decision applying the undue experimentation standard in the context of modern biotechnology inventions. In determining whether undue experimentation negates enablement, Judge Smith emphasized that the key word is "undue", not "experimentation." Id., at 737. Thereafter he applied a standard of reasonableness stating, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id., at 737. In the instant case the Applicant provides the exact amino acid sequence of the H4-1BB protein, provides how it can be derived, provides the cDNA and discusses its use vis-a-vis T-cell proliferation. Once this information is available, (e.g. that we know what H4-1BB is, and

what its precise sequence is) the determination of exact characteristics is routine. Given this, the Examiners rejection for lack of enablement with regard to the H4-1BB does not comport with established patent law precedent and is therefore respectfully traversed. See also, *Hormone Research Foundation, Inc. v. Genentech, Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990)(nonenablement reversed).

Thus, the Examiners concern with regard to the lack of enablement for the specification is misplaced. As has been already pointed out, the techniques surrounding the revelation of the amino acid sequence was known and routine at the time of the application. To do more is not necessary and is actually over-inclusive, as this knowledge forms the body of "known" art that anyone in the field is deemed to both know and have access to. *Spectrea-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987).

The key component of this "precise" recombinant engineering, and other technology, is the cDNA and/or amino acid sequence of interest, here derived from the H4-1BB protein, and disclosed in the application as SEQ. ID. NO.'s: 1 and 2. With the sequence of the target protein (DNA and/or amino acid) in hand, the technology needed for generation of the hybridoma and the subsequent generation of specific antibodies is old, available, and well known to any of those skilled in the art. Given this, the Examiner's rejection under 35 U.S.C. § 112, first paragraph is respectfully traversed, and reconsideration is respectfully requested.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 21, 22, and 24-26 under 35 USC § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. These claims have all been amended to comply with the Examiners concerns. Given the above amendments, the Examiner's rejection under 35 U.S.C.

§ 112, second paragraph is respectfully traversed, and reconsideration is respectfully requested.

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 5-6, 21-22, and 24 under 35 USC § 103, as being unpatentably obvious over Schwarz et al., (CD ROM Deposit of an amino acid sequence) in view of Ayala et al. This rejection is respectfully traversed, and reconsideration is requested.

It must first be pointed out that the "publication" or disclosure which the Examiner points to provide support for her rejection on the basis of obviousness is not one that could be considered sufficient to deny patentability. GenBank deposits are simply the deposit of lists of putative amino acid sequences that themselves mean little or nothing. Especially when first deposited, these lists of amino acids have no associated function, utility, name, or identity attached to them. Far from being enabling disclosures available to the public or workers in the field, these lists are impenetrable unless you already know what you are looking for. In the instance of an novel chain of amino acids (e.g. without an associated identity or function or utility), the no one would be able to use, understand, or inquire about the utility of a given set of amino acids. Thus, this GenBank deposit, by itself has no significance with regard to publication or prior disclosure as identified under existing patent law and specifically CFR 35 USC § 103. To suggest otherwise would be to allow the bare filing of randomly generated amino acid sequences to bar the novelty of later discovered genes, with known functions, utility and application to real world concerns.

In addition to the above, for the Examiner to maintain the obviousness rejection through the use of a bare amino acid, without more (e.g., identity, function, cDNA, or any knowledge of a homologue/analog) is to assert a position that contradicts other Examiner holdings in this most recent Office Action. That is, the Examiners denial of an earlier priority

date in accordance with the parent applications of this file (s/n 07/267,577 (1988); or s/n 07/922,996 (1992)) priority contradicts the Examiners assertions in making this objection. If the 103 rejection, and the specific techniques and journal art cited as rendering the current application obvious, is maintained, then it is logical to state that the prior parent applications are themselves enabling for the amino acid sequences and the uses thereto, and thus the only appropriate priority date is in 1988, certainly the Examiner can agree that the early applications disclosed much more relevant information than the bare sequence published in GenBank (i.e. cDNA, probe fragments, homology comparisons, "pld78" etc.,). When this is done it would eliminate Schwarz as a relevant reference, and obviate the current obviousness rejection. Alternatively, if the parental applications, containing much more relevant information are not considered enabling sufficient to maintain the Applicant's priority, then to state that a bare sequence, which does not correspond exactly, is enabling is illogical.

In this discussion Ayala is considered to be reflective of the general knowledge in the art in the relevant time frames, and thus need not be specifically addressed as inapplicable herein. Respectfully therefore, Applicant believes that this objection is traversed. Reconsideration of this point, and clarification of the Examiners position on the priority issue, is respectfully requested.

It is also important to note that in order for an "obviousness" rejection to be valid it is incumbent upon the Examiner to show that the cited artisans showed some indication that the specific features of prior inventions or modifications could or should be combined to better effect. That is, the art **must** at least indicate that a combination would be possible and desirable in order to render a future combination of that art obvious to one skilled in the relevant field. The fact that both of the cited references fail to do this themselves is clear. For the rejections of claims 5-6, 21-22 and 24, no other art is cited other than Schwarz et al., and Ayala et al., to render these claims obvious. This being the case, the references must stand on their own in their effort to render the recited claims as unpatentably obvious. However, the fact is that the precise sequence of amino acids was not in fact produced by either of the cited

references, nor the specific behavior, function or utility for the H4-1BB protein duplicated, therefore no rejection on the basis of obviousness should be maintained.

It is important to point out that **there is no requirement in patent law that the a patentable product be produced by non-obvious or novel methods,** regardless of whether that product is a hybridoma capable of producing a specific antibody to a species specific protein, a stretch of DNA, or an amino acid sequence but only that the product (e.g. the hybridoma) itself be non-obvious. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); *In re Thorpe*, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985). As an example the Federal Circuit recently upheld this principle in *In re Beers* where the court found that the genes for human insulin like growth factors I and II (IGF) **were not rendered obvious by the previously disclosed full amino acid sequences, similar the Examiner's concern here.** In the instant case there has been no similar product to that claimed by the Applicant and so a rejection based on obviousness is inappropriate.

Applicant believes the claims, as amended, are patentable over the prior art, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicants' attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Respectfully submitted,
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By: _____ May 2, 1997

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